

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

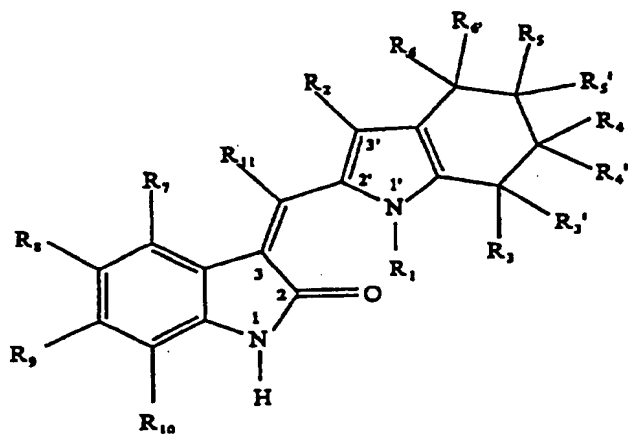
1. – 6. (canceled)

7. (original) An optionally substituted 3-[(tetrahydroindole-2-yl)methylene]-2-indolinone or 3-[(cyclopentano-b-pyrrol-2-yl)methylene]-2-indolinone compound.

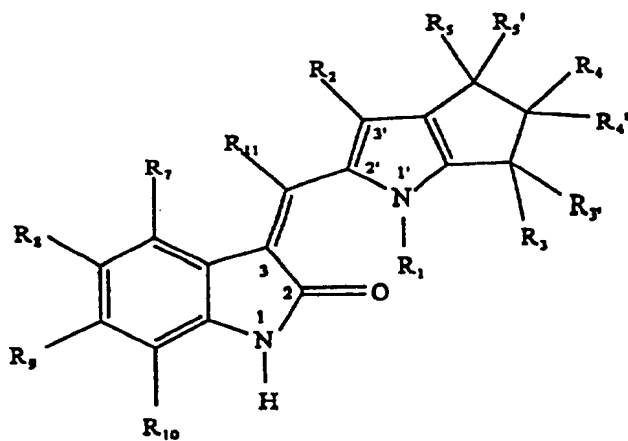
8. (amended) The indolinone compound of claim 7 of formula XIX or

XX,

XIX



XX



or a pharmaceutically acceptable salt, isomer, metabolite, ester, amide, or prodrug thereof
where (a) R₁ is selected from the group consisting of,

- (i) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
- (ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (iii) ketone of formula $-\text{CO}-\text{R}_{12}$, where R_{12} is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (iv) a carboxylic acid of formula $-(\text{R}_{13})_n-\text{COOH}$ or ester of formula $-(\text{R}_{14})_m-\text{COO}-\text{R}_{15}$, where R_{13} , R_{14} , and R_{15} are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and n and m are independently 0 or 1;
- (v) a sulfone of formula $-(\text{SO}_2)-\text{R}_{16}$, where R_{16} is selected from the group consisting of alkyl or a five or six membered heterocyclic ring, where the ring is optionally substituted with an alkyl moiety;
- (vi) $-(\text{R}_{17})_n-(\text{indole-1-yl})$ or $-(\text{R}_{18})_m-\text{CHOH}-(\text{R}_{19})_p-(\text{indole-1-yl})$, where the indole moiety is optionally substituted with an aldehyde and R_{17} , R_{18} , and R_{19} are alkyl and n , m , and p are independently 0 or 1;
- (vii) taken together with a 2' substituent of the indole ring forms a tricyclic moiety, where each ring in the tricyclic moiety is a five or six membered heterocyclic ring;
- (b) R_2 , R_3 , R_3' , R_4 , R_4' , R_5 , R_5' , R_6 and R_6' are selected from the group consisting of,
 - (i) hydrogen;
 - (ii) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;

- (iii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (iv) ketone of formula $-\text{CO}-\text{R}_{20}$, where R_{20} is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (v) a carboxylic acid of formula $-(\text{R}_{21})_n-\text{COOH}$ or ester of formula $-(\text{R}_{22})_m-\text{COO}-\text{R}_{23}$, where R_{21} , R_{22} , and R_{23} are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (vi) halogen;
- (vii) an alcohol of formula $-(\text{R}_{24})_m-\text{OH}$ or an ether of formula $-(\text{R}_{24})_n-\text{O}-\text{R}_{25}$, where R_{24} and R_{25} are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (viii) $-\text{NR}_{26}\text{R}_{27}$, where R_{26} and R_{27} are independently selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;
- (ix) $-\text{NHCOR}_{28}$, where R_{28} is selected from the group consisting of hydroxyl, alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (x) $-\text{SO}_2\text{NR}_{29}\text{R}_{30}$, where R_{29} and R_{30} are selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;
- (xi) any two of R_3 , R_3' , R_4 , R_4' , R_5 , R_5' , R_6 , or R_6' taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the indole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring;
- (c) R_7 , R_8 , R_9 , and R_{10} are independently selected from the group consisting of,
 - (i) hydrogen;

- (ii) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
- (iii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (iv) ketone of formula $-\text{CO}-\text{R}_{31}$, where R_{31} is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (v) a carboxylic acid of formula $-(\text{R}_{32})_n-\text{COOH}$ or ester of formula $-(\text{R}_{33})_m-\text{COO}-\text{R}_{34}$, where R_{32} , R_{33} , and R_{34} are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and n and m are independently 0 or 1;
- (vi) halogen;
- (vii) an alcohol of formula $-(\text{R}_{35})_m-\text{OH}$ or an ether of formula $-(\text{R}_{35})_n-\text{O}-\text{R}_{36}$, where R_{35} and R_{36} are independently chosen from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (viii) $-\text{NR}_{37}\text{R}_{38}$, where R_{37} and R_{38} are independently selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;
- (ix) $-\text{NHCOR}_{39}$, where R_{39} is selected from the group consisting of hydroxyl, alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (x) $-\text{SO}_2\text{NR}_{40}\text{R}_{41}$, where R_{40} and R_{41} are selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;

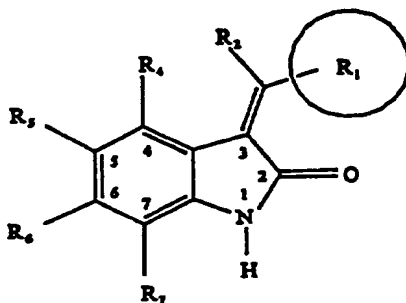
- (xi) any two of R_7 , R_8 , R_9 , or R_{10} taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the indole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring; and
- (d) R_{11} is hydrogen or alkyl.

9. (amended) An indolinone compound having a substituent at the 5 position of the oxindole ring, where the substituent at the 5 position of the oxindole ring is selected from the group consisting of

- (a) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
- (b) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (c) a ketone of formula $-\text{CO}-R_{10}$, where R_{10} is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (d) a carboxylic acid of formula $-(R_{11})_n-\text{COOH}$ or ester of formula $-(R_{12})_m-\text{COO}-R_{13}$, where R_{11} , R_{12} , and R_{13} are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (e) halogen;
- (f) an alcohol of formula $-(R_{14})_m-\text{OH}$ or an ether of formula $-(R_{14})_n-\text{O}-R_{15}$, where R_{14} and R_{15} are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (g) $-\text{NR}_{16}R_{17}$, where R_{16} and R_{17} are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;

- (h) -NHCOR_{18} , where R_{18} is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (i) $\text{-SO}_2\text{NR}_{19}\text{R}_{20}$, where R_{19} and R_{20} are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (j) any two of R_4 , R_5 , R_6 , or R_7 taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the oxindole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring.

10. (amended) The compound of claim 9 of the following formula,



where (a) R_5 is selected from the group consisting of,

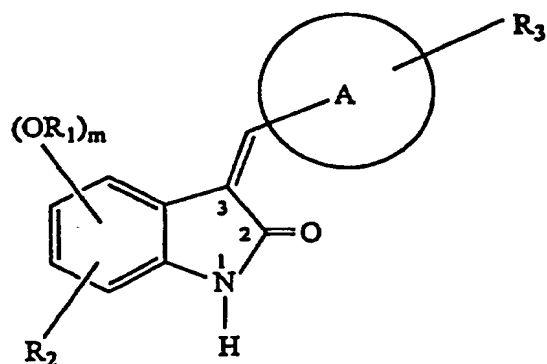
- (i) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;

- (ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (iii) a ketone of formula $-\text{CO}-\text{R}_{10}$, where R_{10} is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (iv) a carboxylic acid of formula $-(\text{R}_{11})_n-\text{COOH}$ or ester of formula $-(\text{R}_{12})_m-\text{COO}-\text{R}_{13}$, where R_{11} , R_{12} , and R_{13} are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (v) halogen;
- (vi) an alcohol of formula $-(\text{R}_{14})_m-\text{OH}$ or an ether of formula $-(\text{R}_{14})_n-\text{O}-\text{R}_{15}$, where R_{14} and R_{15} are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (vii) $-\text{NR}_{16}\text{R}_{17}$, where R_{16} and R_{17} are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (viii) $-\text{NHCOR}_{18}$, where R_{18} is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (ix) $-\text{SO}_2\text{NR}_{19}\text{R}_{20}$, where R_{19} and R_{20} are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (x) any two of R_4 , R_5 , R_6 , or R_7 taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the oxindole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring;
- (b) R_1 is selected from the group consisting of a five, six, eight, nine, and ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more substituents selected from the group consisting of

- (i) hydrogen and alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
 - (ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
 - (iii) a ketone of formula $-\text{CO}-\text{R}_{21}$, where R_{21} is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
 - (iv) a carboxylic acid of formula $-(\text{R}_{22})_n-\text{COOH}$ or ester of formula $-(\text{R}_{23})_m-\text{COO}-\text{R}_{24}$, where R_{22} , R_{23} , and R_{24} are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;
 - (v) halogen;
 - (vi) an alcohol of formula $-(\text{R}_{25})_m-\text{OH}$ or an ether of formula $-(\text{R}_{25})_n-\text{O}-\text{R}_{26}$, where R_{25} and R_{26} are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;
 - (vii) $-\text{NR}_{27}\text{R}_{28}$, where R_{27} and R_{28} are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
 - (viii) $-\text{NHCOR}_{29}$, where R_{29} is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
 - (ix) $-\text{SO}_2\text{NR}_{30}\text{R}_{31}$, where R_{30} and R_{31} are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (c) R_4 , R_6 , and R_7 are independently selected from the group consisting of,

- (i) hydrogen and alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
- (ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (iii) a ketone of formula $-\text{CO}-\text{R}_{32}$, where R_{32} is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (iv) a carboxylic acid of formula $-(\text{R}_{33})_n-\text{COOH}$ or ester of formula $-(\text{R}_{34})_m-\text{COO}-\text{R}_{35}$, where R_{33} , R_{34} and R_{35} are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (v) halogen;
- (vi) an alcohol of formula $-(\text{R}_{36})_m-\text{OH}$ or an ether of formula $-(\text{R}_{36})_n-\text{O}-\text{R}_{37}$, where R_{36} and R_{37} are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (vii) $-\text{NR}_{38}\text{R}_{39}$, where R_{38} and R_{39} are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (viii) $-\text{NHCOR}_{40}$, where R_{40} is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (ix) $-\text{SO}_2\text{NR}_{41}\text{R}_{42}$, where R_{41} and R_{42} are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring; and
- (d) R_2 is hydrogen or alkyl.

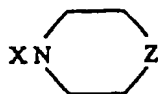
11. (original) A compound having formula XXI, wherein:



XXI

- (a) A is a five or six membered ring comprised of atoms selected from the group consisting of oxygen, carbon, sulfur and nitrogen;
- (b) m is zero, 1, or 2;
- (c) R_1 is hydrogen, C_1 - C_6 alkyl or C_2 - C_6 alkanoyl;
- (d) one of R_2 and R_3 independently is hydrogen and the other is a substituent selected from:
 - (1) a C_1 - C_6 alkyl group substituted by 1, 2 or 3 hydroxy groups;
 - (2) SO_3R_4 in which R_4 is hydrogen or C_1 - C_6 alkyl unsubstituted or substituted by 1, 2 or 3 hydroxy groups;

- (3) SO_2NHR_5 in which R_5 is as R_4 defined above or $\alpha\text{-(CH}_2)_n\text{-N(C}_1\text{-C}_6\text{ alkyl)}_2$ group in which n is 2 or 3;
- (4) COOR_6 in which R_6 is $\text{C}_1\text{-C}_6$ alkyl unsubstituted or substituted by phenyl or by 1, 2 or 3 hydroxy groups or phenyl;
- (5) CONHR_7 , in which R_7 is hydrogen, phenyl or $\text{C}_1\text{-C}_6$ alkyl substituted by 1, 2 or 3 hydroxy groups or by phenyl;
- (6) NHSO_2R_8 in which R_8 is $\text{C}_1\text{-C}_6$ alkyl or phenyl unsubstituted or substituted by halogen or by $\text{C}_1\text{-C}_4$ alkyl;
- (7) $\text{N(R}_9)_2$, NHR_9 or OR_9 wherein R_9 is $\text{C}_2\text{-C}_6$ alkyl substituted by 1, 2 or 3 hydroxy groups;
- (8) NHCOR_{10} , OOCR_{10} or $\text{CH}_2\text{OOCR}_{10}$ in which R_{10} is $\text{C}_1\text{-C}_6$ alkyl substituted by 1, 2 or 3 hydroxy groups;
- (9) NHCONH_2 ; $\text{NH-C(NH}_2\text{)=NH}$; $\text{C(NH}_2\text{)=NH}$; $\text{CH}_2\text{NHC(NH}_2\text{)=NH}$; CH_2NH_2 ; OPO(OH)_2 ; $\text{CH}_2\text{OPO(OH)}_2$; PO(OH)_2 ; or a



wherein X is selected from the group consisting of CH_2 , SO_2 , CO , or $\text{NHCO(CH}_2)_p$ in which p is 1, 2, or 3 and Z is CH_2 , O or N-R_{11} in which R_{11} is hydrogen or is as R_9 defined above.

12. (original) A method of making an indolinone compound of any one of claims 5-11 comprising the steps of reaching an appropriate aldehyde and oxindole and separating the indolinone from the aldehyde and oxindole reactants.

13. (original) A pharmaceutical composition comprising (i) a pharmaceutically acceptable carrier or excipient and (ii) a compound according to any one of claims 5-11.

14. (original) A method for treating a disease related to unregulated tyrosine kinase signal transduction, the method comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound according to anyone of claims 5-11.

15. (original) A method for regulating tyrosine kinase signal transduction comprising administering to a subject a therapeutically effective amount of a compound according to any one of claims 5-11.

16. (original) A method of preventing or treating an abnormal condition in an organism, where the abnormal condition is associated with an aberration in a signal transduction pathway characterized by an interaction between a protein kinase and a natural binding partner, where the method comprises the following steps:

- (a) administering a compound of any one-of claims 5-11 to an organism; and
- (b) promoting or disrupting the abnormal interaction.

17. (original) A method of preventing or treating an abnormal condition in an organism, where the abnormal condition is associated with an aberration in a signal transduction pathway characterized by an interaction between a protein kinase and a natural binding partner, where the method comprises the following steps:

- (a) administering a compound of any one of claims 5-11 to an organism; and
- (b) promoting or disrupting the abnormal interaction.